

Psychotherapy plus antidepressant for panic disorder with or without agoraphobia: a systematic review

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Abstract

Objectives: To review evidence concerning short- and long-term merits and demerits of combined psychotherapy plus antidepressant treatment for panic disorder with or without agoraphobia in comparison with either therapy alone

Design: Systematic review of all relevant randomized controlled trials

Participants and Interventions: 1709 patients in 23 randomised comparisons between psychotherapy (behaviour therapy, cognitive-behaviour therapy, and others) plus antidepressant treatment versus antidepressant alone, psychotherapy alone, or psychotherapy plus placebo treatments

Main outcome measures: The primary outcome was relative risk of “response,” i.e. substantial overall improvement from baseline as defined by the original investigators. Secondary outcomes included standardized weighted mean differences in global severity, panic attack frequency, phobic avoidance, general anxiety, depression, and social functioning, and relative risks of overall dropouts and dropouts due to side effects.

Results: In the acute phase treatment, the combined treatment was consistently superior to either monotherapy (NNT between 7 and 10). It produced more dropouts due to side effects than psychotherapy (NNH around 26). After discontinuation of the acute phase treatment, the combined therapy was as effective as psychotherapy and more effective than antidepressant pharmacotherapy alone (NNT around 6). These effects were most consistent for behaviour therapy and cognitive-behaviour therapy, irregardless of class of antidepressant or presence of agoraphobia.

Conclusions: Appropriate resources should be made available so that either combined therapy or psychotherapy alone can be recommended as first line treatment for panic disorder with or without agoraphobia, depending on the patient’s preferences.

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What is already known on this topic

Both psychotherapy and pharmacotherapy are effective for panic disorder with or without agoraphobia.

In the real world practice they are frequently combined but the short-term and long-term merits and demerits of their combination are not clear. Trials of combination therapy to date have given conflicting results, and existing reviews are unsystematic and/or narrative and give conflicting recommendations.

There are some suggestive findings that adding drugs hurts, i.e. reduces the effectiveness of psychotherapy especially in the long term.

What this study adds

The combined psychotherapy plus antidepressant therapy is more effective than antidepressant alone or psychotherapy alone treatments for the acute phase treatment of panic disorder with or without agoraphobia (NNT between 7 and 10). The combined therapy produces more dropouts due to side effects than psychotherapy plus placebo or psychotherapy alone treatment (NNH around 26).

The combined therapy is as effective as psychotherapy and more effective than antidepressant pharmacotherapy after discontinuation of the acute phase treatment (NNT around 6).

The evidence was most consistent for behaviour therapy and cognitive-behaviour therapy.

Introduction

Panic disorder affects around 2% of the population for any one year and around 2-4% of the population sometime during their lifetime¹. It is estimated to account for 0.5% of the global burden of disease for the humankind in 2002, a percentage figure as great as epilepsy and greater than breast cancer for example².

Two broad categories of treatment have been shown to be effective in treating panic disorder with and without agoraphobia; one is psychotherapy and cognitive-behaviour therapy in particular, and the other is pharmacotherapy with antidepressants and benzodiazepines^{3,4}. It remains to be seen, however, whether combining these two effective forms of treatment confers any additional benefit over and above either of the treatments alone, both in the short and long terms.

It is important to examine this issue for many reasons. Firstly, combination therapy appears to be practiced very frequently in the real world, possibly because 30-50% of patients remain unimproved at the end of acute phase treatment by either monotherapy. Secondly, it is now increasingly recognized that pharmacotherapy alone, by antidepressant or benzodiazepine, tends to result in substantial relapse rates not only when discontinued⁵ but even when maintained at adequate dosage⁶. Cognitive-behaviour therapy is associated with less relapses but may not always be able to prevent them over long term⁷. It is therefore necessary to know the outcomes of the patients after the active treatments.

However, the evidence regarding the incremental effectiveness of combined therapy remains inconclusive. Several reviews can be found in the literature but their conclusions have been variable, with some favoring the combination^{8,9}, some favoring monotherapy^{10,11} and others with mixed or guarded conclusions^{4,12}. Unfortunately most of these reviews have been either unsystematic or narrative only^{4,10,12} or, where meta-analytic summary was essayed, did not focus on head-to-head comparisons^{8,9,11}. The precariousness of comparing different treatment conditions by way of their within-group effect sizes or between-group effect sizes against placebo conditions has been well documented^{13,14}.

Not only is the incremental effectiveness unproven, there is a possibility that combination hurts. Several reports have suggested that benzodiazepines may actually interfere with and detract from cognitive-behavioural interventions^{15,16}. We do not yet know if the same applies to the antidepressant, although there are some suggestive findings¹⁷.

The primary objective of this systematic review is therefore to review and synthesize evidence from randomised controlled trials that examined short- and long-term effects and adverse effects of combined treatment by psychotherapy and antidepressants in comparison with either therapy alone in the treatment of panic disorder with or without agoraphobia. This review focuses on antidepressants, and a separate review is in preparation that focuses on benzodiazepines.

Methods

Inclusion criteria

We included randomised controlled trials comparing the combined psychotherapy and antidepressant pharmacotherapy against either of these single approaches among adult patients with panic disorder with or without agoraphobia.

The following individual or group psychological treatments were included: behaviour therapy which uses some kind of exposure, cognitive therapy which uses some kind of cognitive restructuring, cognitive-behaviour therapy which contains both of cognitive and behavioural therapy elements, and other psychological approaches. We included all commonly prescribed antidepressants.

Studies where irregular use of benzodiazepines took place or where benzodiazepines were regularly administered at a constant dosage for long-time users were included. The effect of this decision was examined in a sensitivity analysis. Studies where benzodiazepines were regularly administered as part of the study medication were excluded.

Our primary outcome was “response,” i.e. substantial improvement from baseline as defined by the original investigators. Examples would be “very much or much improved” according to the Clinical Global Impression Change Scale¹⁸, more than 40% reduction in the Panic Disorder

Severity Scale¹⁹ score, and more than 50% reduction in panic frequency or the Fear Questionnaire Agoraphobia subscale²⁰. Our secondary outcomes included global severity, frequency of panic attacks, phobic avoidance, general anxiety, depression, social dysfunction, patient satisfaction and cost effectiveness.

The total number of dropouts for any reason was regarded as a proxy measure of treatment acceptability. Adverse effects were evaluated by looking at the number of dropouts due to adverse effects.

Identification of trials

We electronically searched the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR) in April 2003, which is a study-based registry of randomised trials incorporating results of group searches of MEDLINE (1966-), EMBASE (1980-), CINAHL (1982-), PsycINFO (1974-), PSYINDEX (1977-) and LILACS (1982-1999) and handsearches of major psychiatric and medical journals. Two complementary searches for additional relevant trials were conducted with the Cochrane Central Register of Controlled Trials (CENTRAL) and with MEDLINE. No language restriction was imposed.

Two reviewers examined titles and abstracts of studies identified by the electronic search strategies and then checked full articles for eligibility. To identify further trials, references of these selected studies and of other review papers were also checked, representative studies were subjected to SciSearch, and authors and experts were contacted.

Quality assessment and data extraction

Two independent reviewers assessed the methodologic quality of the selected studies according to the recommendations of the Cochrane Collaboration Handbook²¹, which emphasises allocation concealment and double blinding (A: low risk of bias, B: moderate risk of bias, C: high risk of bias). In addition to these, we assessed the adequacy of the psychotherapy according to the following criteria. We determined if the administered psychotherapy had demonstrable

effectiveness, if: A, when the psychotherapy alone arm was shown to be superior to the placebo arm in the same trial; B, when the conduct of psychotherapy was examined by a third reviewer through audiotapes etc; and C, when the authors gave some description of the therapy procedure only. The decision to include level C studies was examined in a sensitivity analysis.

Two reviewers independently extracted data from the original reports using data extraction forms. Any disagreement was resolved by consensus between the two or, where necessary, between all three reviewers.

Data synthesis

Data were entered into Review Manager 4.2 and double-checked for accuracy.

For dichotomous outcomes, relative risks and their 95% confidence intervals were calculated using random effects model, because random effects model RR has been shown to be superior in clinical interpretability and external generalizability than fixed effects models and odds ratios or risk differences²². Heterogeneity between studies was assessed by the I-squared statistic and the Q statistic. If significant heterogeneity was noted (I-squared>30% or p<0.10 was taken to be indicative of heterogeneity), sources were investigated. For continuous outcomes, the standardized weighted mean difference (SMD) and their 95% confidence intervals were calculated using random effects model.

For dichotomous outcomes, we used intention-to-treat (ITT) analyses according to the following principle. When data on dropouts were carried forward and included in the efficacy evaluation by the last-observation-carried-forward (LOCF) in the original reports, they were included as such. When dropouts were excluded from any assessment in the primary studies (for example, those who never returned for assessment after randomisation), they were considered to be non-responders in both active and comparison groups. The same principles applied to outcomes at or after end of maintenance treatment, because we were interested in the percentage of patients remaining well among those who had entered the trials at all, and not among those who successfully entered and/or finished the maintenance treatment phase.

Subgroup and sensitivity analyses

We planned the following three a priori subgroup analyses.

- 1) For each type of psychotherapy separately (behaviour therapy, cognitive-behaviour therapy, and psychodynamic therapy and others)
- 2) For classes of antidepressants (tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and others)
- 3) For patients with agoraphobia and for those without agoraphobia

We performed the above-mentioned sensitivity analyses by two methods. First we limited the studies to those with higher quality in terms of allocation concealment, blinding, operational diagnosis, quality control of psychotherapy, and control of benzodiazepine co-intervention.

Second we ran meta-regression²³ to examine if these variables significantly affected the pooled effect sizes.

Results

Description of studies

The electronic search identified 139 studies from CCDANCTR, additional 164 from CENTRAL and 35 from MEDLINE. Browsing their titles and abstracts, 135 articles were identified by either of the two independent reviewers as possible candidates and their full copies were obtained. Two independent reviewers then examined the strict eligibility of these 41 papers.

With further reference search, SciSearch and personal contacts, we identified 21 studies which satisfied the strict eligibility and validity criteria. The inter-rater reliability of the eligibility criteria was percentage agreement of 94%. Because two studies provided two comparisons each^{24,25}, we have 23 comparative studies comprising 1709 participants altogether.

Typically the majority of the participants were women, and their average age was in the 30's.

They had suffered from panic disorder for 5 to 10 years. Only one study¹⁷ focused on patients with panic disorder without agoraphobia, while 13 comparisons²⁴⁻³⁴ focused on patients with

panic disorder with agoraphobia.

The typical length of the acute phase active treatment was between 8 and 12 weeks. Twelve studies administered behaviour therapy consisting of exposure and/or breathing retraining and/or relaxation exercises^{24-27, 29-34}. No study used narrowly-defined cognitive therapy relying only on cognitive restructuring. Nine studies administered cognitive-behaviour therapy consisting of both behaviour and cognitive therapy elements^{17, 28, 35-41}.

With regard to medications, 14 studies used TCA (imipramine in 10, clomipramine in 3, trazodone in 1 study), 7 studies used SSRI (paroxetine in 4, fluvoxamine in 3), and two other studies used monoamine oxidase inhibitors (moclobemide and phenelzine).

No study reported on patient satisfaction or cost issues.

With regard to validity, all but four^{24, 42, 43} of the 23 comparisons scored B for allocation concealment. Nineteen trials scored A, and 4 trials scored C for double blinding^{29, 38, 40, 43}. The inter-rater reliability of these two validity criteria was percentage agreement of 94% for allocation concealment and 83% for double blinding. With regard to quality control of the psychotherapies provided, only three studies scored A^{17, 28, 36}. Four studies scored B, i.e. examined the adequacy of the psychotherapies through audiotapes^{26, 32, 33, 41}.

Four studies acknowledged financial support from pharmaceutical companies^{28, 33, 36, 39}; these companies marketed the drugs involved in the trials. Oehrberg et al³⁵ did not acknowledge financial support from a drug company but three of the co-authors were company employees.

Psychotherapy+Antidepressant vs Antidepressant treatment

Acute phase treatment

Combining 322 patients in the psychotherapy+antidepressant arm and 347 patients in the antidepressant alone arm from 11 studies, the combination arm was 1.24 (95% CI: 1.02 to 1.52) times more likely to produce response at the end of 2-4 months of acute phase treatment than the antidepressant alone arm (Figure 1). There was significant and moderate heterogeneity ($p=0.05$, I-squared=44.9%). Furthermore the funnel plot (Figure 2) was suggestive of some

publication bias, with one small study reporting an extreme result³⁰. Subgroup analyses suggested greater heterogeneity of “psychodynamic and other therapies” category^{42,43} [See below]. When we omitted these studies, thus limiting the included studies to those employing behaviour or cognitive-behaviour therapies, the RR was the same (RR=1.28, 1.08 to 1.52) and there was no longer statistical heterogeneity (p=0.18, I-squared=30.5%) or funnel plot asymmetry.

The superiority of the combination therapy was corroborated by secondary analyses employing continuous data. The combination arm decreased global severity of the disorder (SMD=-0.36, -0.60 to -0.11), depression (SMD=-0.52, -0.76 to -0.28), and social dysfunction (SMD=-0.47, -0.89 to -0.05). Trends in favour of the combination therapy were noted for panic frequency (SMD=-0.20, -0.56 to 0.16), phobic avoidance (SMD=-0.22, -0.59 to 0.14) and general anxiety (SMD=-0.43, -0.88 to 0.03).

There was no difference in the overall dropouts or in the dropouts due to side effects.

Continuation treatment

There was strong heterogeneity (p=0.005, I-squared=76.8%). Limiting the studies to behaviour and cognitive-behaviour therapies, heterogeneity was lost (p=0.55, I-squared=0%) and the combination therapy was 1.63 (1.21 to 2.19) times more likely to produce response than the antidepressant alone treatment, as long as medication was continued.

After treatment termination

Figure 3 shows five studies that reported outcomes after 6-24 months of naturalistic follow-up. Combining outcomes based on 376 participants, the combination therapy was still superior to antidepressant alone (RR=1.61, 1.23 to 2.11). No heterogeneity was noted (p=0.50, I-squared=0%).

Psychotherapy+Antidepressant vs Psychotherapy

Although the comparison psychotherapy+antidepressant vs psychotherapy alone is theoretically different from the comparison psychotherapy+antidepressant vs psychotherapy+placebo⁴⁴, our

meta-analytic summaries for the former comparison were remarkably in line with those for the latter comparison, both for the acute phase and follow-up evaluations, and pooling trials involving and not involving drug placebos did not increase heterogeneity. We therefore report herein the aggregated results of trials comparing psychotherapy+antidepressant vs psychotherapy alone and psychotherapy+placebo.

Acute phase treatment

Comparing 592 patients in the psychotherapy+antidepressant arm and 665 patients in the psychotherapy arm from 19 studies, the former was 1.16 (95% CI: 1.03 to 1.30) times more likely to produce response at the end of acute phase treatment than the latter (Figure 4). The test for heterogeneity was not significant, with I-squared of 10.5%. Funnel plot of response was somewhat suggestive of publication bias, with two small studies reporting results much in favor of the combination therapy^{30, 33}. Excluding them reduced heterogeneity further (I-squared became 2.2%) but the RR was unaffected (1.14, 1.02 to 1.26).

The same superiority of the combined therapy were noted for the global severity (SMD=-0.43, -0.60 to -0.26). Looking at different aspects of panic disorder, although no statistically significant difference was found for frequency of panic attacks, the combination therapy was again significantly superior in terms of reduction in phobic avoidance (SMD=-0.31, -0.49 to -0.12), general anxiety (SMD=-0.41, -0.59 to -0.23), depression (-0.39, -0.59 to -0.20), and social dysfunction (SMD=-0.36, -0.61 to -0.11).

Although the two arms did not differ in overall dropout rates, dropouts due to side effects were more frequent in the combined therapy arm (RR=3.01, 1.61 to 5.63).

Continuation treatment

As long as the treatments were continued, the advantage of the combination therapy appeared to continue, as the response rate at the end of continuation treatment was still in favour of the combination therapy (RR=1.23, 1.00 to 1.51) and the global severity was significantly lower in the combination arm (SMD=-0.65, -0.97 to -0.33).

After treatment termination

658 patients from nine studies were assessed at 6 to 24 months after discontinuing treatment (Figure 5). Any advantage of the combination therapy seems to vanish away because neither the response rate nor the global severity measures was significantly different between the two arms.

Subgroup and sensitivity analyses

1) Types of psychotherapy. For all the outcomes during the acute phase or continuation treatments or after treatment discontinuation, the confidence intervals of the pooled estimates of the effectiveness of behaviour therapy and cognitive-behaviour therapy overlapped to a significant degree (Figures 1, 3-5). Pooling these two kinds of psychotherapies together seldom resulted in significant heterogeneity. The only exception was "Psychodynamic psychotherapy and others" category for the comparison psychotherapy+antidepressant vs antidepressant alone. The results from these studies were sometimes qualitatively different not only from one another but also from the other studies administering behaviour or cognitive-behaviour therapies, and combining them altogether often resulted in significant and substantive heterogeneity.

2) Classes of antidepressants. We performed a meta-analysis of 14 studies which used TCAs and 7 studies which used SSRIs as antidepressants. The pooled estimates of effect size of these two meta-analyses were very similar with each other, and with the overall results in terms of response or global severity (Table).

3) Patients with agoraphobia and those without agoraphobia. We performed a meta-analysis of 13 studies which focused on patients with agoraphobia only. The results were very similar to the overall results and overlapped greatly with the only study which focused on patients without agoraphobia¹⁷ (Table)

Meta-regression of quality variables including allocation concealment, blinding, diagnostic accuracy, quality control of psychotherapy, and control of benzodiazepine co-intervention was not significant, either singly or in combination. Limiting the studies to be included to those with higher quality, we obtained pooled estimates that were qualitatively no different from and essentially identical to the overall results, thus suggesting the robustness of the overall findings.

Discussion

The combined psychotherapy plus antidepressant treatment turned out to be consistently superior to either monotherapy for the acute phase treatment of panic disorder with or without agoraphobia, bringing about better outcomes in most aspects of the disorder including phobic avoidance, general anxiety, depression and social functioning. Taking the average response rates between 50-70% for monotherapy, the pooled RR of 1.2 for the combination therapy will be translated into NNTs between 7 and 10. Psychotherapy produced less dropouts due to side effects than the combination therapy which in turn was no different from antidepressant alone treatment.

The naturalistic follow-up of the included RCTs demonstrated the sustained advantage of the combination therapy over antidepressant therapy for 6-24 months but no differential effectiveness over psychotherapy. At 6-24 months after treatment discontinuation, the combined therapy still showed an NNT around 6 over antidepressant pharmacotherapy. With regard to the comparison between the combination therapy and psychotherapy, it is important to note that, despite recent admonitions from several experts^{10, 12, 45}, no disadvantage was observed for the combination therapy in the long term.

These results were robust against several sensitivity analyses. We also observed similar effectiveness for two of the three a priori defined subgroup analyses, namely for TCAs and SSRIs, and for patients with agoraphobia and those without. In terms of differential effectiveness of various forms of psychotherapy, however, only behaviour therapy and cognitive-behaviour therapy were homogeneously effective; the other therapy modalities produced mixed results which lead to increased heterogeneity. Funnel plot analyses were suggestive of some publication bias. However, excluding outliers and limiting to behaviour and cognitive-behaviour therapies, we were able to arrive at effect estimates which were more homogeneous and yet materially no different from the overall results.

The major strengths of the present systematic review may be as follows. First of all, we

performed systematic and comprehensive search of the relevant trials: we identified 23 comparisons whereas the previous reviews were able to include 11 to 13 studies at maximum^{10, 12, 46}. Secondly, we abode by the ITT principle when meta-analysing dichotomous outcomes by counting all the dropouts as non-responders. This policy is especially pertinent when considering the relative merits of the combination therapy over monotherapy in the long term, because we are interested in the number of patients doing well out of those who started the acute phase therapy and not out of those who successfully completed it. Lastly, the a priori planned sensitivity analyses and subgroup analyses confirmed the overall findings.

Several possible weaknesses of the present study must however be pointed out as well. Firstly, the funnel plot analyses suggested possibility of publication bias among the identified trials. Excluding outliers, however, did not affect the pooled estimates. Secondly, generalisability of the present findings beyond specialist psychiatric settings is not straightforward. Only one study³⁶ was conducted in the primary care setting. However, given the limited availability of qualified cognitive-behaviour therapists, this may not be an important limitation. Even in this study³⁶ patients were seen in their local GP clinics but by qualified clinical psychologists. Thirdly, we must point out that up until recently, there has not been widely accepted and validated rating scales for panic disorder and many studies included in this systematic review used the authors' original scales. There is a study to indicate that rating scales which have not been validated or standardized are more likely to report statistically significant findings⁴⁷. Last but most importantly, the comparability of the treatment arms after termination of acute phase and continuation treatments may be compromised by the naturalistic nature of the follow-ups. Participants were usually free to seek further treatment between treatment termination and follow-up assessments, and between 30 to 77% did receive additional therapies. This does not necessarily undermine the comparability of the treatment arms per se; had the published studies reported number of patients who did well without further treatment, the interpretation of the relative merits of the combination versus single therapies would have been more straightforward.

The following is not, strictly speaking, the weakness of our study because we did not plan our review to answer such questions. However, it must be noted that our review does not answer the question of relative merits of combination versus sequential treatments. Given the present findings, some might argue for psychotherapy alone as first line treatment, and to consider combination therapy only when the former fails; it appears to be a viable option but remains unproven as far as the present review is concerned.

In conclusion, based on the current findings for the available best evidence, either combined therapy or psychotherapy alone may be chosen as first line treatment for panic disorder with or without agoraphobia depending on the patient's preferences and values. Antidepressant pharmacotherapy alone is not to be recommended as first line treatment where appropriate resources are available. Although none of the included studies examined cost issues, naïve economic consideration of years of medication versus one-off psychological treatment would favour inclusion of psychotherapy too.

Two lines of inquiry warrants further investigation. Firstly, in the acute phase treatment, if we adhere to the strict ITT principle, the response rates are only slightly above 50% for combination therapy and slightly below 50% for psychotherapy alone. We need to develop strategies to deal with partial and non-responders to these therapies. Secondly, for the long term outcome, our review suggested that combined psychological plus antidepressant therapy does not interfere with psychotherapy. Further research is necessary to confirm this finding by counting the numbers of patients completely recovered, without further treatment during follow-up.

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Contributors: T A Furukawa developed the idea of this systematic review, did the literature search, study selection, data extraction, and data analysis. N Watanabe did the literature search, study selection and data extraction. R Churchill developed the protocol and helped in the interpretation of the results. All the investigators contributed to the writing of the paper, and act as guarantors.

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Figure 1. Psychotherapy+Antidepressant vs Antidepressant: Response at end of acute phase treatment

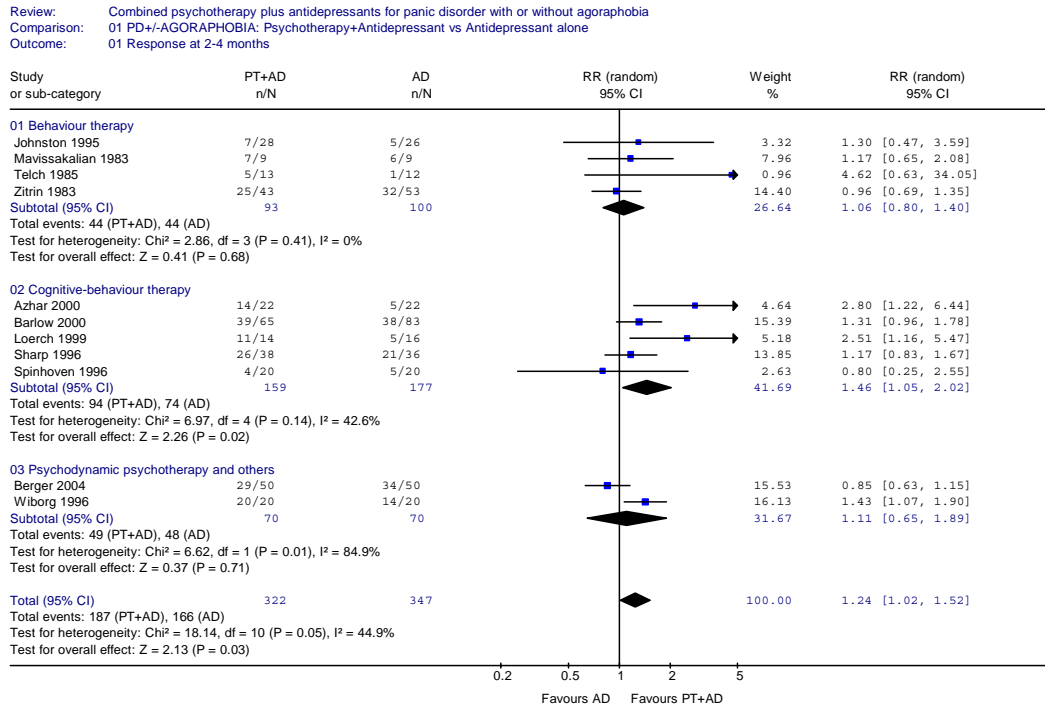


Figure 2. Funnel plot analyses

Review: Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia
Comparison: 01 PD+/-AGORAPHOBIA: Psychotherapy+Antidepressant vs Antidepressant alone
Outcome: 01 Response at 2-4 months

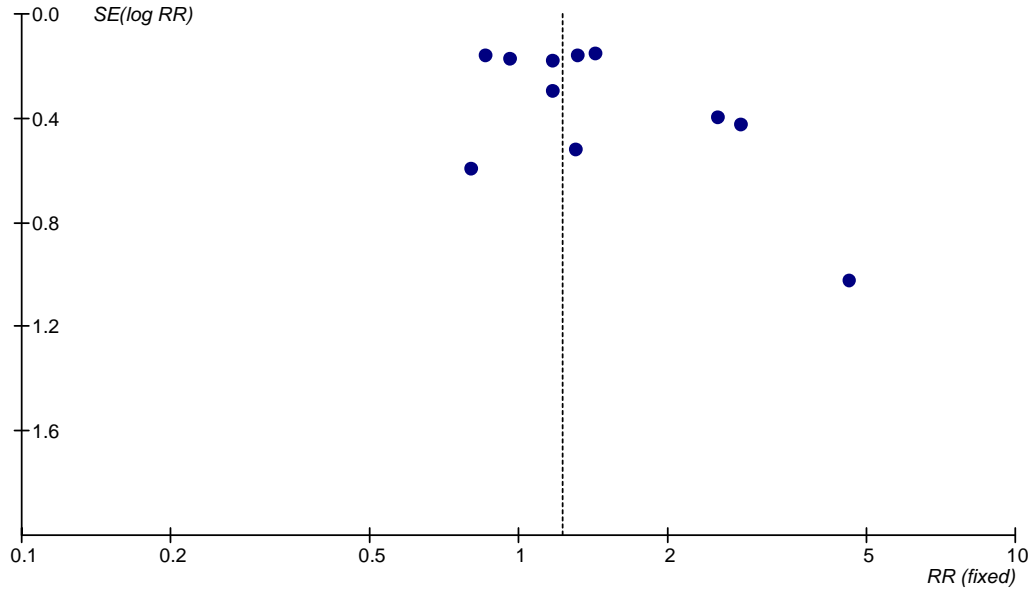


Figure 3. Psychotherapy+Antidepressant vs Antidepressant: Response after treatment termination

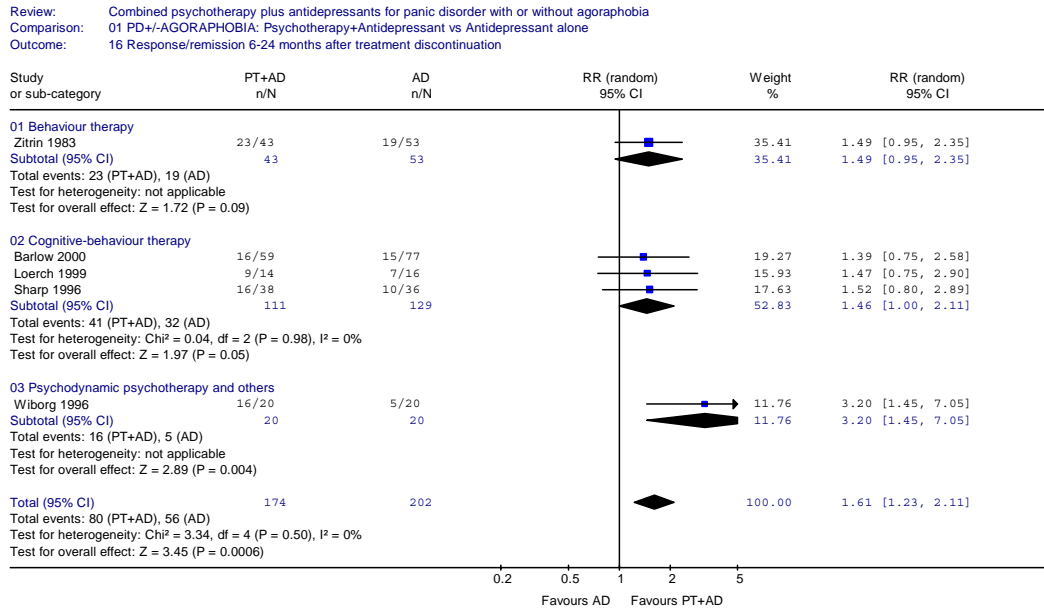


Figure 4. Psychotherapy+Antidepressant vs Psychotherapy: Response at end of acute phase treatment

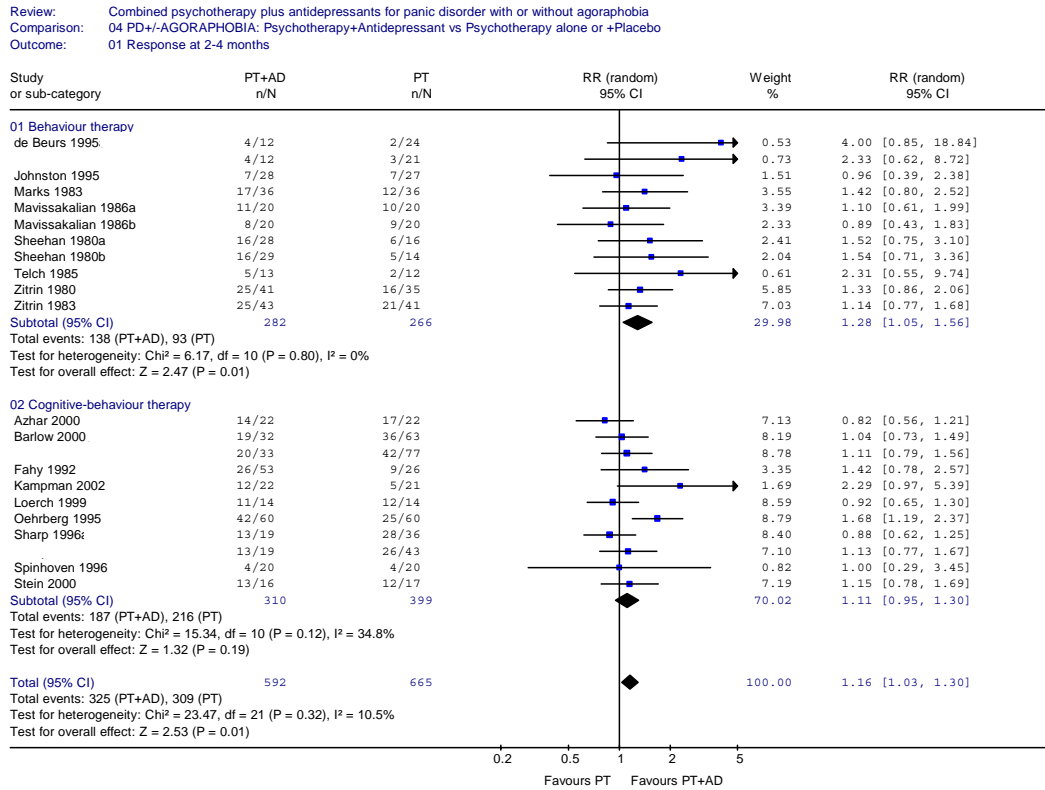


Figure 5. Psychotherapy+Antidepressant vs Psychotherapy: Response after treatment

terminationg

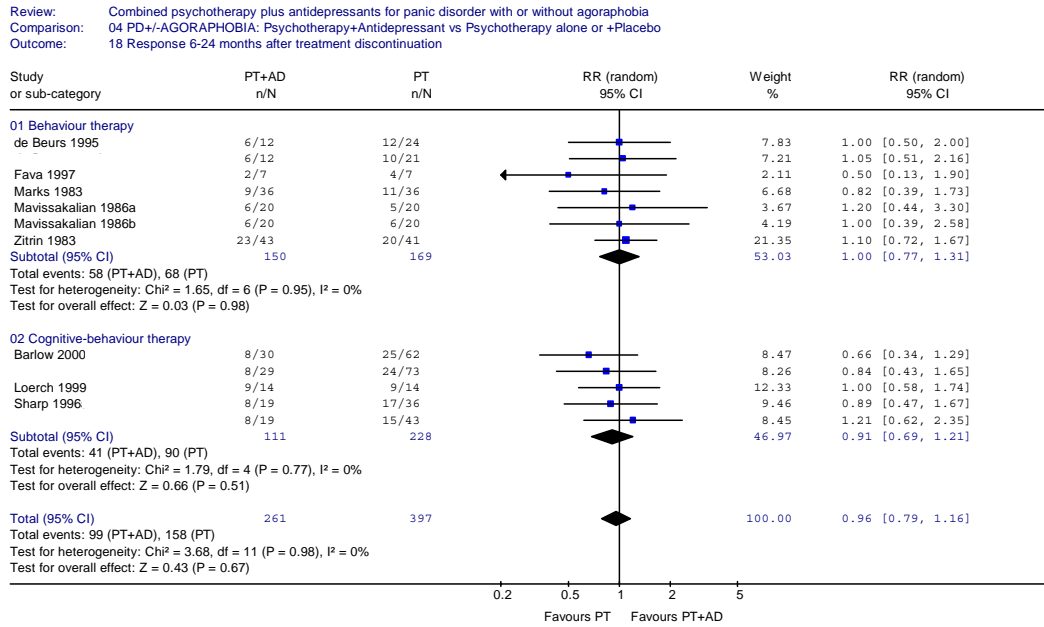


Table. Subgroup analyses

			Overall	TCA	SSRI	With agoraphobia	Without agoraphobia	
vs Antidepressant	Acute phase	Response*	1.24 (1.02 to 1.52)	1.24 (1.05 to 1.46)	1.23 (0.75 to 2.03)	1.35 (0.88 to 2.08)	1.31 (0.96 to 1.78)	
		Severity†	-0.30 (-0.55 to -0.05)	-0.35 (-0.66 to -0.04)	-0.48 (-1.01 to 0.04)	-0.51 (-1.45 to 0.44)	-0.22 (-0.55 to 0.10)	
		After termination	Response*	1.61 (1.23 to 2.11)	1.74 (1.12 to 2.69)	1.52 (0.80 to 2.89)	1.48 (1.02 to 2.17)	1.39 (0.75 to 2.58)
	Severity†	-0.58 (-1.78 to 0.63)	-0.58 (-1.78 to 0.63)	-	-	0.00 (-0.34 to 0.34)		
	vs Psychotherapy	Acute phase	Response*	1.16 (1.03 to 1.30)	1.17 (1.01 to 1.36)	1.24 (0.94 to 1.65)	1.18 (1.00 to 1.40)	1.08 (0.84 to 1.38)
			Severity†	-0.43 (-0.60 to -0.26)	-0.48 (-0.67 to -0.28)	-0.29 (-0.64 to 0.06)	-0.61 (-0.87 to -0.34)	-0.25 (-0.55 to 0.04)
After termination		Response*	0.96	0.91	1.03	1.00	0.74	

	(0.79 to 1.16)	(0.70 to 1.18)	(0.73 to 1.44)	(0.79 to 1.27)	(0.46 to 1.19)
Severity†	0.14	0.16	0.01	0.05	0.21
	(-0.09 to 0.37)	(-0.14 to 0.45)	(-0.56 to 0.58)	(-0.32 to 0.43)	(-0.10 to 0.52)

* Random effects model RR (Values greater than 1.0 denote better outcomes for the combination therapy)

† Random effects model SMD (Negative values denote better outcomes for the combination therapy)